# Restless Legs Syndrome and Risk of Incident Cardiovascular Disease in Women and Men: Prospective Cohort Study

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# Restless legs syndrome and risk of incident cardiovascular disease in women and men: prospective cohort study

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## ABSTRACT

**Objectives:** To evaluate the association between restless legs syndrome (RLS) and incident cardiovascular disease (CVD).

**Design:** Prospective cohort study.

**Setting:** Women's Health Study (WHS) and Physicians' Health Study (PHS), USA.

**Participants:** 29 756 female health professionals aged ≥45 years and 19 182 male physicians aged ≥40 years at baseline.

**Main outcome measures:** Main outcome was incidence of major CVD; secondary outcomes were first incidence of myocardial infarction, stroke, death due to CVD or coronary revascularisation.

**Results:** 3487 (11.7%) women and 1373 (7.2%) men met International Restless Legs Study Group criteria for RLS. In the WHS 450 major CVD events occurred and 1064 major CVD events were confirmed in the PHS. In both cohorts, RLS was not associated with increased risk of major CVD, stroke, myocardial infarction, CVD death or coronary revascularisation. After adjustment for major vascular risk factors, the HRs (95% CI) for major CVD were 1.15 (0.88 to 1.50) in women and 1.01 (0.81 to 1.25) in men. Highest multivariable-adjusted HRs were 1.29 (0.91 to 1.82) for total stroke in women and 1.22 (0.87 to 1.70) for CVD death in men. Excluding participants with comorbidities potentially leading to RLS did not substantially change the effect estimates.

**Conclusions:** In these large prospective studies of female and male health professionals, RLS was not associated with an increased risk of any incident CVD event. The data do not support the hypothesis that RLS is a marker of increased risk of vascular disease.

## ARTICLE SUMMARY

### Article focus

- The aim of this study is to evaluate the association between RLS and incident cardiovascular events in two large prospective cohort studies.

### Key messages

- The results of our two large prospective cohorts do not suggest that either women or men suffering from RLS are at increased risk for any vascular disease event.
- RLS should not be considered a marker for increased CVD risk.

### Strengths and limitations of this study

- Strengths of this study include the large number of participants and outcome events, the prospective study design, the standardised assessment of RLS according to the four minimal diagnostic criteria and confirmation of CVD cases by medical record review.
- The following limitations should be considered: the information on RLS was self-reported and misclassification of cases is possible. No information on frequency, severity and duration of RLS symptoms was available and both cohorts consist of white health professionals, which may limit the generalisability of the results to other populations.

## INTRODUCTION

Restless legs syndrome (RLS) is a movement disorder characterised by an urge to move the legs, typically during rest, and is mostly accompanied by unpleasant leg sensations. This syndrome has been increasingly studied over the last years. According to results from population-based studies, RLS is a common disease with an estimated prevalence ranging from 4% to 29%.[1 2] The prevalence of RLS increases with age, and women are predominately affected. There is increasing evidence that dysfunction of the dopaminergic system is one underlying cause for the syndrome,[3] although the precise mechanisms of this disease are still unknown. In addition, results from genetic studies indicate a genetic predisposition for the disorder.[4 5]

Different comorbidities have been reported to be associated with RLS. Particularly, the

relationship between RLS and prevalent cardiovascular disease (CVD), as suggested by several cross-sectional studies,[6–12] has gained attention due to the high prevalence of both conditions in the general population. In addition, one prospective study from the UK has reported an association between RLS and incident stroke, which was not found for ischaemic heart disease.[13] As potential mechanisms for this relationship, an unfavourable CVD risk factor profile and an elevated activity of the sympathetic nervous system resulting in tachycardia and hypertension have been proposed.[14 15] However, data on the association between RLS and vascular risk factors are inconsistent and studies evaluating the association between RLS and incident CVD are lacking.

Evaluating the association between RLS and CVD is of substantial public health importance because of the high prevalence of RLS. In addition, a relationship between these two diseases would have clinical implications for the management and treatment of patients and would further stimulate research to identify potential common pathophysiological mechanisms. The cross-sectional design of previous studies, however, does not allow determining the direction of association between RLS and CVD and prospective data are lacking. We therefore sought to evaluate the association between RLS and risk of incident CVD in two large prospective cohort studies, the Women's Health Study (WHS) and the Physicians' Health Study (PHS).

## METHODS

### Study populations

The design and methods of both cohorts have been described in detail previously.[16–19] Briefly, the WHS was a randomised placebo-controlled trial designed to test the risks and benefits of low-dose aspirin and vitamin E in the primary prevention of CVD and cancer among apparently healthy women. A total of 39 876 US female healthcare professionals aged 45 years or older at study entry (1992–1995) without a history of CVD, cancer or other major illnesses were randomly assigned to receive active aspirin (100 mg on alternate days), active vitamin E (600 IU on alternate days), both active agents or both placebos. Baseline information was self-reported and collected by a mailed questionnaire that asked about many cardiovascular risk factors and lifestyle variables. Twice in the first year and yearly thereafter, participants were sent follow-up questionnaires asking about study outcomes and other information during the study period. After the termination of the trial in March 2004, the women who were still alive and willing to participate entered an observational follow-up. The return date of the 108-month questionnaire containing questions on RLS was defined as new baseline for this analysis. Of the 33 092 women in active follow-up at 108 months, we excluded 1722 women with missing RLS information, 1614 women who reported CVD events (myocardial infarction, stroke, CVD death, coronary revascularisation) and angina prior to receiving the 108-months questionnaire, leaving a total of 29 756 women free of CVD or angina for this analysis.

The Physicians' Health Study I (PHS I) was a randomised, double-blind placebo-controlled trial to test the benefits and risks of low-dose aspirin (325 mg) and β-carotene (50 mg) in the primary prevention of CVD and cancer among 22 071 apparently healthy physicians aged 40–84 years at baseline in 1982. Baseline information was self-reported and collected by means of a mailed questionnaire that asked about many cardiovascular risk factors and lifestyle variables. Every 6 months in the first year and yearly thereafter, follow-up questionnaires were sent to the participants. Since the trials' termination in 1995, the men are continued to be followed either on an observational basis or as part of the Physician's Health Study II (PHS II).

The PHS II was launched in 1997. The PHS II is an ongoing randomised, double-blind placebo-controlled trial to test the effects of vitamin C (500 mg), vitamin E (400 IU), β-carotene (50 mg) and a daily multivitamin (Centrum Silver) in the prevention of total and prostate cancer, CVD and age-related eye disease among 14 641 US male physicians aged 55 years and older, including a total of 7,641 PHS I participants who were willing and eligible to enter the PHS II. Baseline information was self-reported, and follow-up information was collected annually by mailed questionnaires. For the purpose of this analysis, we pooled data from the PHS I and PHS II, yielding a total of 29 071 participants. The return date of the questionnaire containing the RLS question (216-month questionnaire for PHS I participants and 12-month questionnaire for PHS II participants) was defined as new baseline for this analysis. At this time point, 24 505 men were still in active follow-up. We excluded 1579 men with missing RLS questionnaire information and 3744 men with CVD events and angina prior to the RLS assessment, leaving a total of 19 182 men free of angina and CVD at our defined baseline for our analysis.

All participants of the WHS and the PHS provided written informed consent, and the institutional review board of Brigham and Women's Hospital, Boston, MA, approved the studies as well as the analyses presented here.

### Assessment of RLS

RLS is diagnosed by presence of specific symptoms, and the diagnostic criteria have been established by the International Restless Legs Study Group (IRLSSG). We have implemented standardised questions in both cohorts addressing the four minimal diagnostic criteria of the IRLSSG. Participants were asked: "Do you have unpleasant leg sensations (like crawling, paraesthesias or pain) combined with a motor restlessness and an urge to move?", "Do these symptoms occur only at rest and does moving improve them?", "Are these symptoms worse in the evening or at night compared with the morning?" Participants who answered yes to all the three questions were defined as having RLS. This questionnaire has been established[20–22] and validated[23] in previous studies from

Germany and Italy. Comparing the questionnaire-based diagnosis of RLS with a physician's diagnosis as a gold standard showed good agreement (unweighted $\kappa$=0.67, p<0.001).[23]

### Outcome ascertainment

Participants of both cohorts were asked to report the occurrence of cardiovascular events including myocardial infarction and stroke during follow-up. In addition, information on coronary revascularisation procedures (bypass surgery and percutaneous coronary angioplasty) was collected. Medical records were obtained for all cardiovascular events including coronary revascularisation in the WHS and for all cardiovascular events, but not for coronary revascularisation, in the PHS and were reviewed by an end points committee of physicians. The occurrence of myocardial infarction was confirmed if symptoms met WHO criteria and if the event was associated with abnormal levels of cardiac enzymes or diagnostic ECG. Non-fatal stroke was confirmed if the participant had a new focal neurological deficit of sudden onset and vascular origin that persisted for more than 24 h. Stroke was classified into its major subtypes based on available clinical and diagnostic test information, including brain scans with excellent inter-rater agreement.[24 25] Cardiovascular deaths were confirmed by reviews of autopsy reports, death certificates, medical records and information obtained from next of kin or other family members. Major CVD was defined as a combined end point of non-fatal stroke, non-fatal myocardial infarction or death from CVD events.

### Statistical analysis

We analysed the association between RLS and incident CVD separately in both studies. Baseline characteristics were compared with respect to RLS status using the t-test for continuous and the $\chi^2$ test for categorical variables.

Person-time was calculated from the return date of the questionnaire containing the RLS questions (baseline for this study) to the date of first incident CVD event, non-CVD death, last documented contact or end of the study, whatever occurred first. Information on cardiovascular risk factors and other covariates was updated from the start of the cohorts until the assessment of RLS.

Cox proportional hazards models were used to evaluate the association between RLS and the various CVD events. We calculated age- and multivariable-adjusted HRs and their corresponding 95% CIs. The multivariable-adjusted models accounted for age, randomised aspirin assignments, history of hypertension (yes/no) history of diabetes (yes/no), history of cholesterol level ≥240 mg/dl (yes/no), parental history of myocardial infarction before the age of 60 years (yes/no), alcohol consumption (rarely/never, 1–3/month, 1–6/week, ≥1/day), smoking status (never, past, current), body mass index (BMI) (<25, 25–29.9, ≥30 kg/m$^2$), exercise (WHS: rarely/never, <1/week, 1–3/week, ≥4/week; PHS: rarely/never, ≤1/week, 2–4/week, 5–7/week), history of migraine (yes/no) and postmenopausal hormone use (WHS: never, past, current). Additional adjustment for race, geographic location, depression, iron supplementation use, Parkinson's disease, snoring (PHS only), sleep duration (PHS only), fatigue (WHS only), number of pregnancies (WHS only), age at menarche (WHS only), postmenopausal status (WHS only), oral contraceptive use (WHS only) and analgesic use including aspirin, non-steroidal anti-inflammatory drugs, acetaminophen (WHS only) and aspirin containing drugs (WHS only) did not change the effect estimate of RLS on any CVD event by more than 10%.

A missing value indicator was incorporated in the outcome models for covariates if the number of participants with missing information was ≥100. We assigned participants with missing values to the covariate reference category if the number of missing information was <100. No covariate in the primary analysis had more than 4% missing.

We evaluated effect modification by age (<60, 60–<70, 70–<80, ≥80 years), iron supplementation use (yes/no), BMI (<25 kg/m$^2$, 25–29.9 kg/m$^2$, ≥30 kg/m$^2$), smoking status (never, past, current), history of hypertension (yes/no), fatigue (WHS only) and number of pregnancies (WHS only). Effect modification was tested by including an interaction term for RLS and the potential effect modifier to the outcome model.

The proportional hazards assumption was tested by including an interaction term for RLS status and logarithm of follow-up time for major CVD in age-adjusted models. We found no statistically significant violation.

We performed a sensitivity analysis by excluding participants with a history of polyneuropathy, kidney disease, liver disease, liver cirrhosis (PHS only), rheumatoid arthritis, intermittent claudication and participants who underwent peripheral artery disease surgery. The information on these covariates was updated from the start of the cohorts until assessment of the questionnaire addressing RLS.

For all analyses, we used SAS (V.9.1.3, SAS Institute Inc.). All p values were two tailed, and p<0.05 was considered statistically significant.

## RESULTS

### Baseline characteristics

The baseline characteristics of participants according to RLS status are presented in table 1 for the WHS and in table 2 for the PHS. The prevalence for RLS was 11.7% among women and 7.2% among men. In contrast to the WHS, we observed an age difference according to RLS status in the PHS. Men with RLS had a mean age of 67.8 years and were older than men without RLS. Compared with participants without RLS, both male and female RLS sufferers were more likely to report a history of hypertension, a history of diabetes and a history of hypercholesterolaemia. With regard to lifestyle factors, participants with RLS were more likely to have a BMI ≥30 kg/m$^2$, to rarely/never drink and to rarely/never

**Table 1** Baseline characteristics according to RLS status in the WHS (n=29 756)

| | No RLS (n=26 269) | RLS (n=3487) | p Value |
|---|---|---|---|
| Demographic information | | | |
| Mean age, years (SD) | 63.4 (6.9) | 63.3 (6.8) | 0.30 |
| Ethnicity, n (%) | | | |
| White | 24 786 (95.1) | 3376 (97.4) | <0.01 |
| Geographic location, n (%) | | | <0.01 |
| Northeast | 5168 (19.7) | 605 (17.4) | |
| Southeast | 5985 (22.8) | 825 (23.7) | |
| Midwest | 9362 (35.7) | 1312 (37.7) | |
| West | 5713 (21.8) | 742 (21.3) | |
| CVD risk factors, n (%) | | | |
| History of hypertension | 12 273 (46.7) | 1759 (50.4) | <0.01 |
| History of diabetes | 1709 (6.5) | 295 (8.5) | <0.01 |
| History of cholesterol ≥240 mg/dl | 13 850 (52.8) | 2013 (57.8) | <0.01 |
| BMI categories (kg/m$^2$) | | | <0.01 |
| <25 | 10 813 (41.8) | 1302 (37.8) | |
| 25–29.9 | 8866 (34.3) | 1195 (34.7) | |
| ≥30 | 6177 (23.9) | 950 (27.6) | |
| Smoking status | | | <0.01 |
| Never | 13 484 (52.0) | 1619 (47.0) | |
| Past | 10 352 (39.9) | 1504 (43.7) | |
| Current | 2083 (8.0) | 321 (9.3) | |
| Alcohol consumption | | | 0.05 |
| Rarely/never | 11 071 (42.4) | 1558 (44.9) | |
| 1–3 drinks per month | 3044 (11.7) | 394 (11.3) | |
| 1–6 drinks per week | 8969 (34.4) | 1138 (32.8) | |
| ≥1 drink/day | 2936 (11.2) | 314 (9.0) | |
| Exercise | | | <0.01 |
| Rarely/never | 9875 (37.6) | 1380 (39.6) | |
| <1/week | 5224 (19.9) | 728 (20.9) | |
| 1–3 times/week | 8225 (31.3) | 1064 (30.5) | |
| ≥4 times/week | 2939 (11.2) | 314 (9.0) | |
| Parental history of myocardial infarction | 4391 (16.8) | 646 (18.6) | <0.01 |
| Postmenopausal status | | | 0.13 |
| Premenopausal | 467 (1.8) | 54 (1.6) | |
| Postmenopausal | 23 368 (90.8) | 3082 (90.1) | |
| Biological uncertain | 1651 (6.4) | 253 (7.4) | |
| Unclear/subject unsure | 264 (1.0) | 33 (0.96) | |
| Postmenopausal hormone use | | | <0.01 |
| Never | 5626 (22.3) | 636 (18.9) | |
| Past | 6347 (25.2) | 836 (24.9) | |
| Current | 13 225 (52.5) | 1891 (56.2) | |
| Other covariates, n (%) | | | |
| History of migraine | 5509 (21.0) | 909 (26.1) | <0.01 |
| History of depression | 3132 (11.9) | 707 (20.3) | <0.01 |
| History of Parkinson's disease | 105 (0.4) | 21 (0.6) | 0.08 |
| Iron supplementation use | 1028 (4.0) | 124 (3.6) | 0.30 |
| Being fatigued | 9101 (34.8) | 1776 (51.1) | <0.01 |

Percentages may not add up to 100% due to rounding or missing values.
BMI, body mass index; CVD, cardiovascular disease; RLS, restless legs syndrome; WHS, Women's Health Study.

exercise in both cohorts. In addition, both male and female RLS sufferers more frequently reported a history of depression and migraine.

## Risk of CVD

### Women's Health Study

A total of 450 first major CVD events, 176 myocardial infarctions, 245 strokes, 66 CVD deaths and 461 coronary revascularisations were confirmed during a mean follow-up of 6.0 years. Age- and multivariable-adjusted HRs (95% CI) for the association between RLS and the various vascular events are presented in table 3. Women with RLS had an increased age-adjusted HR of 1.42 (1.10 to 1.82) for coronary revascularisation. The association was diminished and became insignificant after adjustment for vascular risk factors. RLS was not associated with a significantly increased risk for major CVD, myocardial infarction, stroke or CVD death.

**Table 2** Baseline characteristics according to RLS status in the PHS (n=19 182)

| | No RLS (n=17 809) | RLS (n=1373) | p Value |
|---|---|---|---|
| Demographic information | | | |
| Mean age, years (SD) | 66.6 (8.7) | 67.8 (8.9) | <0.01 |
| Ethnicity, n (%) | | | |
| White | 16 091 (90.8) | 1288 (94.2) | <0.01 |
| Geographic location, n (%) | | | 0.16 |
| Northeast | 3983 (22.4) | 299 (21.8) | |
| Southeast | 5137 (28.8) | 359 (26.2) | |
| Midwest | 4547 (25.5) | 375 (27.3) | |
| West | 4031 (22.6) | 329 (24.0) | |
| Other | 111 (0.6) | 11 (0.8) | |
| CVD risk factors, n (%) | | | |
| History of hypertension | 8596 (48.3) | 703 (51.2) | 0.04 |
| History of diabetes | 1200 (6.7) | 138 (10.1) | <0.01 |
| History of cholesterol ≥240 mg/dl | 8387 (47.1) | 686 (50.0) | 0.04 |
| BMI categories (kg/m$^2$) | | | <0.01 |
| <25 | 7550 (42.5) | 519 (37.8) | |
| 25–29.9 | 8197 (46.1) | 665 (48.5) | |
| ≥30 | 2038 (11.5) | 189 (13.8) | |
| Smoking status | | | 0.17 |
| Never | 9763 (54.9) | 719 (52.4) | |
| Past | 7543 (42.4) | 617 (45.0) | |
| Current | 495 (2.8) | 37 (2.7) | |
| Alcohol consumption | | | <0.01 |
| Rarely/never | 3120 (17.5) | 292 (21.3) | |
| 1–3 times/month | 2171 (12.2) | 157 (11.4) | |
| 1–6 times/week | 6631 (37.3) | 514 (37.4) | |
| ≥1 times/day | 5862 (33.0) | 410 (29.9) | |
| Exercise | | | <0.01 |
| Rarely/never | 6174 (34.8) | 536 (39.2) | |
| ≤1/week | 455 (2.6) | 39 (2.9) | |
| 2–4 times/week | 7917 (44.6) | 594 (43.4) | |
| 5–7 times/week | 3204 (18.1) | 200 (14.6) | |
| Parental history of myocardial infarction | 1910 (10.7) | 137 (10.0) | 0.39 |
| Other covariates, n (%) | | | |
| History of migraine | 2157 (12.1) | 202 (14.7) | <0.01 |
| History of depression | 1709 (9.8) | 219 (16.1) | <0.01 |
| History of Parkinson's disease | 207 (1.2) | 20 (1.5) | 0.33 |
| Iron supplementation use | 298 (1.9) | 25 (2.1) | 0.73 |
| Sleep duration ≥8 h | 5254 (32.7) | 431 (34.9) | 0.11 |
| Snoring | | | 0.24 |
| Never | 4382 (26.9) | 338 (27.0) | |
| A few nights | 6604 (40.6) | 482 (38.5) | |
| Most nights | 5283 (32.5) | 433 (34.6) | |

Percentages may not add up to 100% due to rounding or missing values.
BMI, body mass index; CVD, cardiovascular disease; PHS, Physician's Health Study; RLS, restless legs syndrome.

### Physicians' Health Study

In table 4, age- and multivariable-adjusted HRs (95% CI) for the association between RLS and vascular outcomes in the PHS are summarised. During a mean follow-up of 7.3 years, 1064 major CVD events, 431 myocardial infarctions, 381 strokes and 389 CVD deaths were confirmed. In addition, 1352 coronary revascularisations were reported. RLS at baseline was not associated with incident vascular events in age-adjusted or multivariable-adjusted models.

### Sensitivity analyses

After excluding participants with comorbid conditions that have been associated with RLS, the lack of association between RLS and our outcome events remained robust, with the exception of stroke in the WHS. The multivariable-adjusted HR increased from 1.29 (0.91 to 1.82) to 1.42 (0.99 to 2.05).

In both cohorts, the effect estimates did not change by more than 5% when excluding a history of diabetes from the list of confounding factors in multivariable-adjusted models.

### Effect modification

The associations between RLS and major CVD were not significantly modified by age (p for interaction in the WHS: 0.12, p for interaction in the PHS: 0.51), BMI (p

**Table 3** Age- and multivariable-adjusted HRs for incident vascular events according to RLS status in the WHS

| | Primary analysis (n=29 756) | | Sensitivity analysis* (n=27 649) | |
|---|---|---|---|---|
| | No RLS history (n=26 269) | Any history of RLS (n=3487) HR (95% CI) | No RLS history (n=24 472) | Any history of RLS (n=3177) HR (95% CI) |
| Major cardiovascular event | n=386 | n=64 | n=338 | n=56 |
| Age adjusted | 1.00 | 1.25 (0.96 to 1.63) | 1.00 | 1.27 (0.96 to 1.69) |
| Multivariable adjusted† | 1.00 | 1.15 (0.88 to 1.50) | 1.00 | 1.18 (0.89 to 1.57) |
| Any stroke | n=207 | n=38 | n=178 | n=35 |
| Age adjusted | 1.00 | 1.39 (0.98 to 1.96) | 1.00 | 1.51 (1.05 to 2.16) |
| Multivariable adjusted† | 1.00 | 1.29 (0.91 to 1.82) | 1.00 | 1.42 (0.99 to 2.05) |
| Myocardial infarction | n=153 | n=23 | n=138 | n=20 |
| Age adjusted | 1.00 | 1.13 (0.73 to 1.75) | 1.00 | 1.11 (0.69 to 1.77) |
| Multivariable adjusted† | 1.00 | 1.01 (0.65 to 1.57) | 1.00 | 1.00 (0.62 to 1.59) |
| Coronary revascularisation | n=388 | n=73 | n=346 | n=59 |
| Age adjusted | 1.00 | 1.42 (1.10 to 1.82) | 1.00 | 1.30 (0.99 to 1.72) |
| Multivariable adjusted† | 1.00 | 1.24 (0.96 to 1.59) | 1.00 | 1.14 (0.86 to 1.50) |
| CVD death | n=57 | n=9 | n=52 | n=6 |
| Age adjusted | 1.00 | 1.21 (0.60 to 2.45) | 1.00 | 0.90 (0.39 to 2.09) |
| Multivariable adjusted† | 1.00 | 1.11 (0.55 to 2.25) | 1.00 | 0.85 (0.36 to 1.98) |

*2107 women with polyneuropathy, liver disease, kidney disease/failure, peripheral artery disease surgery, intermittent claudication and rheumatoid arthritis were excluded from the analysis.
†Adjusted for age, randomised treatment assignments, history of hypertension, history of diabetes, history of hypercholesterolaemia, parental history of myocardial infarction, history of migraine, alcohol consumption, body mass index, smoking, exercise and postmenopausal hormone use.
CVD, cardiovascular disease; RLS, restless legs syndrome; WHS, Women's Health Study.

for interaction in the WHS: 0.72, p for interaction in the PHS: 0.28), smoking status (p for interaction in the WHS: 0.71, p for interaction in the PHS: 0.43), iron supplementation use (p for interaction in the WHS: 0.75, p for interaction in the PHS: 0.35), history of hypertension (p for interaction in the WHS: 0.76, p for interaction in the PHS: 0.43), fatigue (p for interaction WHS: 0.91) or number of pregnancies (p for interaction WHS: 0.92).

## DISCUSSION

In this study, evaluating data from two large prospective cohort studies of women and men, RLS was not associated with an increased risk for incident vascular events

**Table 4** Age- and multivariable-adjusted HRs for incident vascular events according to RLS status in the PHS

| | Primary analysis (n=19 182) | | Sensitivity analysis* (n=15 625) | |
|---|---|---|---|---|
| | No RLS history (n=17 809) | Any history of RLS (n=1373) HR (95% CI) | No RLS history (n=14 578) | Any history of RLS (n=1047) HR (95% CI) |
| Major cardiovascular event | n=974 | n=90 | n=755 | n=61 |
| Age adjusted | 1.00 | 1.09 (0.88 to 1.35) | 1.00 | 1.03 (0.79 to 1.33) |
| Multivariable adjusted† | 1.00 | 1.01 (0.81 to 1.25) | 1.00 | 0.96 (0.74 to 1.25) |
| Any stroke | n=357 | n=24 | n=271 | n=18 |
| Age adjusted | 1.00 | 0.77 (0.51 to 1.17) | 1.00 | 0.82 (0.51 to 1.33) |
| Multivariable adjusted† | 1.00 | 0.73 (0.48 to 1.11) | 1.00 | 0.79 (0.49 to 1.28) |
| Myocardial infarction | n=392 | n=39 | n=315 | n=25 |
| Age adjusted | 1.00 | 1.23 (0.88 to 1.71) | 1.00 | 1.06 (0.70 to 1.59) |
| Multivariable adjusted† | 1.00 | 1.12 (0.80 to 1.55) | 1.00 | 0.97 (0.64 to 1.45) |
| Coronary revascularisation | n=1239 | n=113 | n=976 | n=87 |
| Age adjusted | 1.00 | 1.15 (0.95 to 1.40) | 1.00 | 1.22 (0.98 to 1.52) |
| Multivariable adjusted† | 1.00 | 1.06 (0.88 to 1.29) | 1.00 | 1.12 (0.90 to 1.40) |
| CVD death | n=350 | n=39 | n=260 | n=25 |
| Age adjusted | 1.00 | 1.27 (0.91 to 1.77) | 1.00 | 1.17 (0.78 to 1.77) |
| Multivariable adjusted† | 1.00 | 1.22 (0.87 to 1.70) | 1.00 | 1.13 (0.75 to 1.70) |

*3557 men with a history of polyneuropathy, kidney disease, liver disease, liver cirrhosis, rheumatoid arthritis, intermittent claudication and men who underwent peripheral artery disease surgery were excluded.
†Adjusted for age, randomised treatment assignments, history of hypertension, history of diabetes, history of hypercholesterolaemia, parental history of myocardial infarction, history of migraine, alcohol consumption, body mass index, smoking and exercise.
CVD, cardiovascular disease; PHS, Physician's Health Study; RLS, restless legs syndrome.

including major CVD, myocardial infarction, stroke, coronary revascularisation and CVD death. Excluding participants with comorbidities that have been associated with RLS did not substantially change our results.

### Comparison with other studies

In contrast to our results, findings from several cross-sectional studies have suggested a relationship between RLS and prevalent CVD.[6–12] Among the 3422 participants of the Sleep Heart Health Study, those with RLS had multivariable-adjusted OR (95% CIs) of 2.05 (1.38 to 3.04) for CVD and 2.07 (1.43 to 3.00) for coronary artery disease. Winkelman *et al*[12] additionally report an association between severity and frequency of RLS and CVD. Compared with those without RLS, participants who reported a RLS frequency of 16–23/month had an OR of 3.53 (1.85 to 6.76) for CVD. Duration of disease was not related to CVD. In our cohorts, data on frequency and severity of symptoms were not available and we had no information about the duration of disease.

Two studies from Sweden, one analysing a random sample of the female population of central Sweden aged 18–64 years and the other one evaluating a comparable random sample of men with the same age range, report an association between RLS and self-reported heart disease.[9 10] As in our study, RLS was defined according to IRLSSG diagnostic criteria in these studies and the observed overall prevalences were comparable to those in our cohorts. The multivariable-adjusted OR for heart disease was 2.13 (1.18 to 3.86) in the female Swedish cohort and 2.5 (1.4 to 4.3) in the study evaluating the random sample of Swedish men.

In the Caerphilly cohort of 1986 men, RLS was associated with incident stroke (multivariable-adjusted OR of 1.67 (1.07 to 2.06)). In addition, the authors report an increased but not significant OR of 1.24 (0.89 to 1.74) for incident ischaemic heart disease events. While we do not find an association between RLS and stroke in out main analysis, the sensitivity analysis suggests potential increased risk for stroke (RR 1.42 (0.99 to 2.05)). RLS was not defined according to IRLSSG diagnostic criteria and the associations were not adjusted for important vascular risk factors including hypertension and diabetes, which are potential limitations of this study.[13]

One cross-sectional study using data from the Burden of Obstructive Lung Disease Initiative in Iceland and Sweden is in line with our finding.[26] A random sample of adults aged 40 years and older was drawn from the national registries in both countries. Benediktsdottir *et al* found a significant higher prevalence of RLS in Icelandic women compared with those from Sweden. In multivariable-adjusted models, RLS, defined according to IRLSSG criteria, was not associated with CVD, assessed by a structured interview, in this study.

A high percentage of RLS patients report periodic limb movements during sleep (PLMS), and PLMS are considered as supportive clinical feature of RLS.[27] The association between periodic limb movements and incident CVD has been recently evaluated among 2911 men aged ≥65 years who participated in the Outcomes of Sleep Disorders in Older Men Sleep Study.[28] Periodic limb movements were assessed by two indices, the periodic limb movement index and the periodic limb movement arousal index. After 4.4 years of mean follow-up, men with a periodic limb movement arousal index ≥5 had a multivariable-adjusted HR of 1.26 (1.01 to 1.56) for all-cause CVD compared with those with the lowest index category. The periodic limb movement index was not statistically significant associated with all-cause CVD (HR 1.25, 95% CI 1.00 to 1.56), which was defined as a composite end point of coronary heart disease, cerebrovascular disease and peripheral artery disease. When evaluating the different end points separately, incident peripheral artery disease was the only CVD event that was significantly associated with one of the indices in multivariable-adjusted models (HR 2.00, 95% CI 1.14 to 3.49). Although PLMS is frequently reported by RLS sufferers, it is not exclusively related to RLS and occurs in other sleep-related disorders and medical conditions. Since the frequency of RLS sufferers could not be determined in the previous mentioned study, the results cannot be translated to a RLS population and the comparability of these results to our study is limited.

RLS can be distinguished in idiopathic and secondary forms. A variety of disorders have been identified to be associated with secondary RLS including anaemia, iron deficiency, rheumatoid arthritis, polyneuropathies and reduced renal function. La Manna *et al* evaluated the association between RLS and incident CVD events among 100 end-stage kidney disease patients who were on dialysis three times a week.[29] After 18 months of follow-up, patients with secondary RLS had an increased risk for CVD events (myocardial infarction, stroke or peripheral artery occlusion), which, however, did not reach statistical significance. In addition, patients with RLS had higher fibrinogen levels, albumin levels, white blood cell counts and higher overall mortality, suggesting that RLS status could be an indicator for poorer health status. Since the study analysed a very distinct population, the comparability of these results with studies in healthier populations including ours is limited.

A possible explanation for the discrepancy between our results and those of previous studies is the prospective cohort design, which allows the assessment of incident CVD cases. Thus, while RLS does not seem to be a risk factor for subsequent CVD, it might be an indicator of a poor health status due to the presence of several, especially cardiovascular, comorbidities.

### Strengths and limitations

Our study has several strengths including the large number of participants in both cohorts, large number of outcome events, prospective design and standardised assessment of RLS according to the four minimal diagnostic criteria of the IRLSSG. Furthermore, incident

CVD events were confirmed by medical record review. In addition, information on many comorbidities and lifestyle factors was available allowing us to adjust for potential confounders.

The following limitations should be considered when interpreting our results. First, information on RLS was self-reported and potential misclassification is possible. However, the questionnaire has been successfully used and validated in previous cohorts from Germany and Italy, and the prevalences of RLS in both cohorts are similar to those reported in other population-based studies.[1] Furthermore, both cohorts consist of health professionals and previous studies indicate that participants with a health profession accurately report information.[30] Moreover, we have excluded participants with comorbidities potentially mimicking RLS syndromes in sensitivity analysis and the results were largely unchanged. Second, we had no information on frequency, severity and duration of RLS symptoms. Third, residual and unmeasurable confounding remains possible as our study is observational. However, we are not aware of any factor that, if controlled for, would establish an association between RLS and CVD. Fourth, both of our cohorts consist of predominately white health professionals, which may limit generalisability to other populations. However, we have no reason to believe that potential biological associations between RLS and CVD are different in our compared with other populations.

## Clinical implications

Results of these two large prospective studies do not suggest that RLS is a marker for increased risk of CVD independent of other cardiovascular risk factors. However, our data also indicate that the prevalence of RLS increases with several comorbidities including traditional CVD risk factors like BMI, hypertension and diabetes. Therefore, patients diagnosed with RLS should be carefully screened for relevant comorbidities and subsequently treated.

## Unanswered questions and future research

RLS is a complex disease and the mechanisms underlying the disease have not been fully understood yet. Understanding the role of diverse comorbidities for the onset of RLS would be an important research target for the future in order to establish strategies to prevent the disease.

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**Author footnote**
Access to data: All authors had full access to all the data in the study and can take responsibility for the integrity of the data and accuracy of the data analyses.

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